REMARKS

Claims 1-3, 5-8, 10, 11, and 51-59 are pending in the present application. Claim 1 has been amended, support for which can be found at, for example, page 116, lines 2-7 of the specification. No new matter has been added. Upon entry of the present amendment, claims 1-3, 5-8, 10, 11, and 51-59 will remain pending.

I. The Claimed Embodiments are Novel and Not Obvious

A. The Landers Reference

Claim 1 is rejected under 35 U.S.C. §102(b) or §103(a) as being anticipated by or obvious over Landers *et al.* (Cancer Research, 1997, 57, 3562-3568, hereinafter, the "Landers reference). The Office Action asserts that the Landers reference discloses a mdm2 primer at page 3563 that is the reverse complement to bases 1796-1775 of Applicants' SEQ ID NO:1. Applicants respectfully request reconsideration in view of amended claim 1.

To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995). Further, to serve as an anticipation when a reference is silent about the alleged inherent characteristic, such gap in the reference may be filled by extrinsic evidence. Such evidence, however, must make clear that the missing descriptive matter is necessarily (*i.e.*, always) present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Oelrich*, 40 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991). Inherency may not be established by probabilities or possibilities. *Id.* Further, the mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Id.* Indeed, inherency must be certain. *Ex parte Cyba*, 155 U.S.P.Q. 756, 757 (Bd. Pat. App. Int. 1966).

Claim 1 has been amended to recite, in part, an antisense compound that "modulates the expression of mdm2 by at least 60%." The Landers reference fails to explicitly disclose an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region, or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein the antisense compound modulates

the expression of mdm2 by at least 60%. Although the primer referred to in the Landers reference may hybridize to mdm2, the Landers reference is silent as to what functional properties the primer may have, if any. The Office Action has not established that the inherent characteristic (i.e, having at least 60% inhibitory activity) is necessarily present in the primer reported in the Landers reference. Therefore, the Landers reference fails to disclose every element of the claim. Accordingly, the Landers reference fails to anticipate the claimed invention.

To set forth a legally sufficient *prima facie* case of obviousness, the prior art must provide motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Lalu*, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Moreover, the Examiner must show that the cited references teach or suggest a claimed invention with a reasonable expectation of success. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988).

The Landers reference fails to render Applicants' claimed invention obvious. Indeed, the Landers reference fails to discuss or even suggest a compound that would modulate the expression of mdm2 by at least 60%. For the Landers reference to render claim 1 obvious there must be some teaching within the reference that would **impel** the skilled artisan to make the present invention. The Office Action fails to point out any motivation to use the PCR primer reported in the Landers reference as a compound for inhibiting the expression of human mdm2.

Even if one skilled in the art were motivated to use the PCR primer of the Landers reference as a compound for inhibiting expression of human mdm2 (and Applicants maintain that such is not the case), a skilled artisan would not have a reasonable expectation of success of inhibiting by at least 60% upon reading the Landers reference. The Landers reference does associate a change in the expression of mdm2 with the presence of the protein HPV-16 E6. Further, there are numerous examples in the present specification whereby the expression of mdm2 is modulated by oligomeric compounds by less than 60% (see, for example, Table 13, pages 113-116). Thus, even if one skilled in the art tried the PCR primer of the Landers reference, there is no reasonable expectation of success.

Therefore, since the Landers reference does not teach modulating the expression of mdm2 using compounds of the present invention, and does not provide the requisite motivation

for one of skill in the art to make and use the invention, the Landers reference does not render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) and 35 U.S.C. § 103(a) be withdrawn.

B. The Combination of the Burrell, Branch and Monia References

Claims 1-3 and 6-8, 10, and 11 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of International Application No. WO 93/20238 (hereinafter, the "Burrell reference"), Branch, *TIBS*, **1998**, *23*, 45-50 (hereinafter, the "Branch reference") and U.S. Patent No. 5,872,242 (hereinafter, the "Monia reference"). The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to design antisense oligonucleotides having at least 17 nucleobases, as reported in the Branch reference, based upon the entire 2372 nucleobase transcript of human MDM2, as reported in the Burrell reference, and further modify the oligonucleotides to maximize target specificity, increase hybridization efficiency, and maintain nuclease resistance, as reported in the Monia reference. Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references and, even if combined, the claimed invention would not be produced.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from appellants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of

> the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to combine particular teachings of the cited references and achieve the claimed invention.

The only motivation identified in the Office Action for applying particular teachings of the Branch and Monia references to the entire 2372 nucleobase transcript of human MDM2 of the Burrell reference is to design oligonucleotides having at least 17 nucleobases "comprising the modifications taught by Monia *et al.* since oligonucleotides of this size possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides." (see, Office Action at pages 10-11). This motivation, however, in no way would lead one skilled in the art to combine the teachings of these references, let alone combine the teachings of these references in the manner suggested in the Office Action. Whether or not the claimed compounds hybridize only to mdm2 nucleic acid molecules and/or modulate the expression of only MDM2 (*i.e.*, maximize target site specificity) is irrelevant. Indeed, Applicants' claims do not recite or require any amount of target specificity for the antisense compounds. Further, even if "a high target site specificity" was desired, then one skilled in the art would use the entire antisense sequence because it has the highest degree of "target site specificity."

Furthermore, as amended, claim 1 now requires that the expression of mdm2 be modulated by at least 60%. The references do not provide a motivating force to make and use compounds that modulate the expression of mdm2 by at least 60%. Even, if there was a motivating force to combine the references, which there is not, the combination does not yield the present invention. None of the references alone or in combination discuss or suggest compounds that modulate expression of mdm2 by at least 60%. The references also do not give the skilled artisan an expectation of success in making and using compounds that modulate expression of mdm2 by at least 60%. There is no expectation of success on the part of the skilled

artisan because numerous compounds could be made and used and fail to modulate the expression of mdm2 by at least 60%. The data in Table 13 of the present specification further demonstrate there can be no expectation of success. There are a total of 72 compounds listed in the Table and 40 (i.e., 55.5%) of the 72 compounds do not modulate the expression of mdm2 by at least 60 %. In fact, 13 (18%) of the compounds modulate the expression of mdm2 by less than 5%. Therefore, as Applicants' data indicates, one skilled in the art would not have a reasonable expectation of success that one of ordinary skill in the art could make and use a compound that modulates the expression of mdm2 by at least 60%.

It appears that a particular element was picked from the Burrell reference (the entire 2372 nucleobase transcript of human MDM2), one particular element from the Branch reference (at least 17 nucleobases) and particular elements from the Monia reference (oligonucleotide modifications) from the many elements recited in the references and combined in a specific manner to replicate Applicants' claimed invention. Indeed, it appears that the only guide to picking and choosing particular elements from the cited references appears to have been the present application. Thus, the combination of cited references is improper for its use of hindsight reconstruction based upon Applicant's disclosure. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

> virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no***

> ***knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed . . .
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2d 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 U.S.P.Q.2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis added).

The general statement that it would be obvious to combine teachings of particular references to design antisense oligonucleotides is unavailing. Such a statement, at best, is an invitation for further experimentation and, at most, provides an "obvious to try" situation. However, "obvious to try" is not the standard of 35 U.S.C. §103. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

C. The Combination of the Burrell and Bennett References

Claims 5 and 51-59 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Burrell reference in view of U.S. Patent No. 6,172,216 (hereinafter, the "Bennett reference). The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to have modified the entire 2372 nucleobase transcript of the Burrell reference to design antisense oligonucleotides having 8-30 nucleobases targeted to particular regions of a nucleic acid encoding human mdm2, wherein at least one 2'-O-methoxyethyl modification is in a cytidine, as allegedly reported in the Bennett reference). Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references and, even if combined, the claimed invention would not be produced.

The Bennett reference reports antisense modulation of BCL-x expression. The Bennett reference fails to cure the many deficiencies of the Burrell reference stated above. For example,

the Bennett reference fails to discuss modulating the expression of human mdm2 by any amount, let alone at least 60%. The Office Action points to no teachings in either the Burrell or Bennett references that would have motivated the skilled artisan to make and use the present invention. Not only does the combination of the references not yield the present invention, but the references and the knowledge of the skilled artisan would not have given an "expectation of success" in making and using compounds that modulate the expression of mdm2 by at least 60%. Even if the compounds reported in the Bennett reference modulate the expression of BCL-x by at least 60%, it does not provide a reasonable expectation of success because each gene is different and its accessibility and percentage of modulation cannot be known until the experiments have been performed. As discussed above, many compounds that did not modulate the expression of mdm2 by at least 60% are disclosed in the present application, which reinforces the concept that there can be no comparison between genes. Indeed, the teachings of inhibition of one gene, particularly the levels of inhibition, have no bearing on the inhibition of another gene, particularly an unrelated gene.

Thus, the references cited by the Office fail to provide motivation or a reasonable expectation of success. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Declaration of Dr. Bennett Under 37 CFR §1.132

Applicants submit herewith a declaration of Dr. Bennett, one of skill in the art of oligonucleotide technology. In paragraphs 3 and 5, Dr. Bennett declares that the level of inhibition of expression for one target with one set of oligonucleotides is not currently predictive of whether a different set of oligonucleotides targeted to a different gene or mRNA will elicit the same level of inhibition of expression. Indeed, the studies described in paragraph 4 and Exhibits A and B support the position taken in paragraphs 3 and 5.

III. Obviousness-Type Double Patenting

Claims 1-3, 6-8, 10 and 11 remain rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,248,921

(hereinafter, the "'921 patent") and over claims 1-20 of U.S. Patent 6,184,212 (hereinafter, the "'212 patent"). Applicants traverse the rejection and respectfully request reconsideration because the claimed invention is not obvious.

Although Applicants disagree with the analysis set forth in the Office Action, to further advance prosecution of the present application, Applicants submit herewith terminal disclaimers, thereby rendering the present rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection under the doctrine of obviousness-type double patenting be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6928 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

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